## REMARKS

Claims 127-137 are currently pending. Claims 1-126 were previously cancelled.

Objection to the Abstract

The Abstract is objected to for not pertaining to the claimed invention. In order to expedite prosecution, applicants have amended the Abstract to refer to methods for identifying aptamer regulators. Support for the amended Abstract may be found, for example, in paragraphs 27-28, 41-43 and 70-107, and in Figures 8-10 of the Specification so no new matter has been added. Accordingly, withdrawal of this objection is respectfully requested.

Objection to the Title

The Title is objected to for not being descriptive. Applicants disagree. Applicants amended the Title in their August 4, 2008 filing (an RCE) to recite "Methods for Identifying Aptamer Regulators". Applicants submit that the current title is descriptive of the claimed invention. Accordingly, withdrawal of this objection is respectfully requested.

Objection to the Specification

The Specification is objected to for not using trademarked terms properly. Specifically, the examiner states that the generic terminology "*in vitro* aptamer selection process" should accompany SELEX™ wherever it appears in the Specification. The term SELEX has been trademarked to identify the source or origin of a variety of products and services. However, none of the trademarked terms relate to the *in vitro* aptamer selection process. Applicants' use of SELEX™ in the Specification was in error. In order to expedite prosecution, applicants have

amended paragraphs 19, 27, 28, 46, 47, 50, 53, 54, 56, 57 and 58, and the text between paragraphs 45 and 46 of the Specification to change SELEX™ to SELEX. SELEX is an acronym for Systematic Evolution of Ligands by EXponential enrichment. No new matter has been added by the deletion of the ™ symbol. Accordingly, withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 127-130, 136 and 137 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lupold *et al.* (U.S. Patent No. 6,933,114).

Applicants respectfully disagree.

According to *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007) and M.P.E.P. § 2141, the framework for the objective analysis for determining obviousness under 35 U.S.C. § 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Obviousness is a question of law that is based upon underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

1) determining the scope and content of the prior art;

2) ascertaining the differences between the claimed invention and the prior art; and

3) resolving the level of ordinary skill in the pertinent art.

Objective evidence relevant to the issue of obviousness, if present, must also be evaluated. Such evidence, sometimes referred to as "secondary considerations", may include evidence of commercial success, long-felt but unsolved needs, failure of others and unexpected results.

The claimed invention is not obvious in view of the cited reference.

*The Claimed Invention*

Independent claim 127 recites a method for identifying an aptamer regulator comprising the steps: providing a target and a target partner that do not bind to each other in the absence of an aptamer regulator; contacting a mixture of nucleic acids with the target and the target partner under conditions that disfavor efficient binding between the target and the target partner; partitioning nucleic acids bound to a target-target partner complex from unbound nucleic acids; and retaining the nucleic acids bound to the target-target partner complex, thereby identifying an aptamer regulator that binds to a target wherein binding of the aptamer regulator to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator such that binding of the aptamer regulator to the target is a prerequisite for target-target partner complex formation.

*Scope and Content of the Cited Art*

Lupold *et al.* ("Lupold") discloses a method for identifying aptamers to Prostate Specific Membrane Antigen (PSMA), and aptamers to PSMA. The method used for identifying such aptamers is called SELEX, an acronym for Systematic Evolution of Ligands by EXponential enrichment. SELEX is a method for the *in vitro* evolution of nucleic acid molecules with highly specific binding to target molecules that comprises the steps of binding nucleic acids to a target, partitioning target bound nucleic acids from unbound nucleic acids, dissociating the bound nucleic acids from the target, and amplifying the nucleic acids that were bound to the target. The Lupold method is the first application of SELEX to a membrane tumor antigen.

*Differences Between the Claimed Invention and the Cited Art*

Independent claim 127, and the claims that depend therefrom, is directed to a method for identifying an aptamer regulator that binds to a target, wherein binding of the aptamer regulator to the target increases the binding affinity of the target for a target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator. Independent claim 127 also recites that the target and the target partner do not bind to each other in the absence of an aptamer regulator, and that binding of the aptamer regulator to the target is a prerequisite for target-target partner complex formation. Therefore, the binding of the aptamer regulator to the target enables the binding of the target to the target partner.

The examiner states that Lupold suggests that the basic aptamer selection method has been modified to achieve specific objectives, and further suggests aptamers having desirable functions, such as facilitating the reaction between a target and another molecule. The examiner further states that "facilitating the reaction between a target and another molecule" means the same as the claim limitation of "an aptamer regulator that binds to a target wherein the binding increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer regulator" in the instant claims.

Assuming, arguendo, that the examiner is correct, that is not applicants' invention. Applicants' invention is not directed to an aptamer regulator. Rather, applicants' invention is directed to a method for identifying an aptamer regulator. Applicants' claimed method comprises specific steps for identifying aptamer regulators.

Lupold discloses the basic SELEX process of binding, partitioning, dissociating and amplifying. In addition, Lupold discloses that the basic SELEX method has been modified to

achieve a number of specific objectives. However, Lupold does not disclose a variation or modification of SELEX to identify an aptamer where the aptamer facilitates the reaction between a target and another molecule. Lupold, in his definition of "nucleic acid ligand" or "aptamer", states that aptamers have desirable actions, such as facilitating the reaction between a target and another molecule. No other teaching or suggestion regarding such facilitation is provided in Lupold. In particular, Lupold does not disclose or suggest a method for identifying aptamers (*i.e.*, aptamer regulators) that facilitate the reaction between a target and another molecule. Accordingly, applicants disagree with the examiner that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Lupold so as to further include, in each method step, a target partner that does not bind the target without an agonist like the aptamer regulator. Modifications to a method can not be obvious based upon a desirable action of an aptamer, as there is no nexus between the desirable action of the aptamer and steps to identify such an aptamer. In addition, applicants' claimed method uses conditions that disfavor binding, which is the opposite of what is disclosed or suggested in Lupold.

Furthermore, applicants agree with the examiner that Lupold does not disclose a target partner and the desired functional activity of the aptamer binding to the target to increase the binding affinity for the target for the target partner relative to the unbound target.

*Level of Ordinary Skill in the Pertinent Art*

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited reference and the claimed invention in view of the *Graham* factors, the cited reference does not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 131-133 and 135 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lupold *et al.* (U.S. Patent No. 6,933,114) in view of Geiger *et al.* (Nucleic Acids Research, vol. 24, no. 6, pp. 1029-1036 (1996)).

Applicants respectfully disagree.

*The Claimed Invention*

Dependent claim 131 recites that the method further comprises a negative selection.

Dependent claim 132 recites that the negative selection comprises the steps:

1) contacting a mixture of nucleic acids with the target partner under conditions that favor specific binding between the nucleic acids and the target partner; and 2) partitioning the bound nucleic acids from the unbound nucleic acids, and retaining the unbound nucleic acids; wherein the unbound nucleic acids are then contacted with the target and the target partner in step b).

Dependent claim 133 recites that the method further comprises the step of removing the retained nucleic acids from the target-target partner complex.

Dependent claim 135 recites that the retained nucleic acids from the target-target partner complex are removed by contacting the bound nucleic acids with excess free target.

*Scope and Content of the Cited Art*

The Lupold reference was discussed above in response to the previous rejection.

Geiger *et al.* ("Geiger") discloses RNA aptamers that bind to L-arginine with sub-micromolar dissociation constants and high enantioselectivity, and a method for identifying such aptamers. The method is a modified *in vitro* selection scheme. The method in Geiger starts with either a completely randomized RNA pool or a degenerate pool of RNA. The RNA is loaded onto a pre-selection column and eluted onto a selection column. The pre-selection column is then removed. Non-binding and low affinity binding RNAs are removed by a buffer wash, an affinity elution with 20 mM citrulline, a heat denaturation/renaturation in 20 mM citrulline, and a wash with 20 mM arginine. RNAs that still bind to the column are heat denatured and renatured in 20 mM arginine in binding buffer, eluted with 20 mM arginine/buffer, phenol extracted and reverse transcribed. The cDNA is PCR-amplified, and the PCR-DNA *in vitro* transcribed to yield an enriched RNA pool that can be used for the next selection cycle.

*Differences Between the Claimed Invention and the Cited Art*

Applicants agree with the examiner that Lupold does not disclose a negative selection or the step of eluting nucleic acids with excess free target.

Geiger, in combination with Lupold, does not disclose or suggest applicant's claimed invention. That is, nothing in Geiger discloses or suggests agonist SELEX, which is a method wherein aptamers are isolated on the basis of their ability to specifically drive association of a target with a target partner. For example, the Geiger method does not disclose or suggest binding target, target partner and nucleic acids under conditions that disfavor binding. On the other hand, Geiger discloses a modified *in vitro* selection scheme that identifies aptamers with sub-micromolar dissociation constants and high enantioselectivity. Geiger does not even contemplate aptamer regulators or methods for identifying aptamer regulators. In addition, the method in Geiger utilizes a negative selection step, a counter-SELEX step, and two

denaturation/renaturation steps. The only things that the claimed method and the Geiger method have in common is: 1) both methods utilize SELEX or a modified version thereof, 2) both methods utilize a negative selection step and 3) both methods utilize an elution step with excess free target. Even though Geiger discloses a negative selection step and an elution step, Geiger does not disclose that such a negative selection step and such an elution step could be used in another method, such as the claimed method. Lastly, the Geiger method is specific for identifying RNA aptamers that bind to arginine, and is not a general method that can be used to identify aptamers to many different targets.

This rejection only relates to dependent claims. For the reasons stated above and for the reasons stated in response to the previous rejection, Geiger, when combined with the teachings of Lupold, does not cure the deficiencies of Lupold.

*Level of Ordinary Skill in the Pertinent Art*

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

Applicants submit that after analyzing the cited references and the claimed invention in view of the *Graham* factors, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 133 and 134 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lupold *et al.* (U.S. Patent No. 6,933,114) in view of Firer *et al.* (J. Biochem. Biophys. Methods, vol. 49, pp. 433-442 (2001)).

Applicants respectfully disagree.

*The Claimed Invention*

Dependent claim 133 recites that the method further comprises the step of removing the retained nucleic acids from the target-target partner complex.

Dependent claim 134 recites that the retained nucleic acids from the target-target partner complex are removed by eluting the nucleic acids with an agonist competitor to the target.

*Scope and Content of the Cited Art*

The Lupold reference was discussed above in response to the first rejection.

Firer ("Firer") is a review article that discloses the elution of functional proteins in affinity chromatograpy. Specifically, Firer examines the chemical effect of various elution buffers on protein-protein interactions in the context of affinity chromatography and examines strategies that may be used for selection of an appropriate buffer.

*Differences Between the Claimed Invention and the Cited Art*

Applicants agree with the examiner that Lupold does not disclose eluting nucleic acids with an agonist competitor to a target.

The examiner states that Firer discloses the strategy of competitive elution with excess ligands from a target molecule immobilized to a resin in a chromatography column.

Applicants disagree.

Page 438, third complete paragraph, of Firer recites:

> An alternative to elution buffers is to use competitive elution by washing the column with excess ligand. This strategy has several advantages including the retention of column-binding capacity due to the mild elution conditions, specificity of elution, especially when there is suspicion of non-specific binding of mobile phase components to the solid matrix and the use of the elution step to study protein-protein interaction. Competitive elution also has its drawbacks. For instance, depending on the ligand, it may not be possible, practical or economic to use the large molar excesses of ligand sometimes required for elution. In

addition, as the effect depends on the $K_d$ of the receptor-ligand interaction, competitive elution may take longer than with most buffers.

It is easy to see that Firer discloses competitive elution with excess ligand, and not an agonist competitor, as is required by the claims.

For the reasons stated above, applicants disagree with the examiner's statement that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the selection method disclosed by Lupold so as to further include the step of eluting the nucleic acids with an agonist competitor to displace the nucleic acid ligands bound to the target, as suggested by Firer. The passage cited by the examiner discloses competitive elution with excess ligand. Excess ligand is not an agonist competitor to the target. An agonist competitor would be a molecule that is different from the ligand to a target.

Furthermore, this rejection only relates to dependent claims. For the reasons stated above and for the reasons stated in response to the first rejection, Firer, when combined with the teachings of Lupold, does not cure the deficiencies of Lupold.

*Level of Ordinary Skill in the Pertinent Art*

Applicants submit that a person having ordinary skill in the art would be a college educated scientist. Such a person would have the capability of understanding the scientific principles applicable to the pertinent art.

Summary

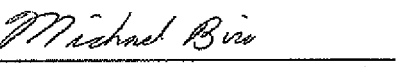
Applicants submit that after analyzing the cited references and the claimed invention in view of the *Graham* factors, the cited references do not render obvious the claimed invention. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

## CONCLUSION

Applicants submit that the claims are not obvious in view of the cited references. Accordingly, reconsideration of the rejections and allowance of the claims at an early date are earnestly solicited.

If there are any questions regarding this Response or if the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



Michael G. Biro, Reg. No. 46,556
Sr. Patent Attorney
Archemix Corp.
300 Third Street
Cambridge, MA 02142
Direct: (617) 475-2324
Main: (617) 621-7700
Fax: (617) 621-9300

Jennifer A. Karnakis, Reg. No. 53,097
Attorney for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, MA 02111
Direct: (617) 348-1618
Main: (617) 542-6000
Fax: (617 542-2241
**Customer No. 69262**